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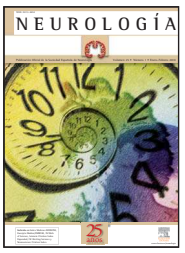

ORIGINAL ARTICLE

Descriptive analysis of the use of atypical antipsychotics under compassionate-use in a health area in Ferrol (La Coruña, Spain)

D. Santos-García[a,*], M. Macías[a], A. Casás-Martínez[b], M. Llaneza[a], J. Abella[a], A. Aneiros[a], H. Santos[a], G. Domínguez-Urbistondo[b] and B. Salazar-Laya[b]

[a] *Sección de Neurología, Hospital A. Marcide, Ferrol, La Coruña, Spain*
[b] *Servicio de Farmacia, Hospital A. Marcide, Ferrol, La Coruña, Spain*

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KEYWORDS
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Anti-psychotic;
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Quetiapine

Abstract
Background and objective: Although atypical antipsychotics (AA) provoke fewer extra-pyramidal symptoms (ES) than classic antipsychotics, their use in patients greater than or equal to 75 years old with dementia must be under compassionate-use. This is an important limitation. We performed a descriptive analysis of the use of atypical antipsychotics under compassionate-use (AACU) in the Ferrol health area.
Patients and methods: We retrospectively assessed all the patients who were receiving an AACU from March, 2004 (that is the date when prescription under compassionate-use of AA came into force in Spain) to 30 November, 2008.
Results: One hundred and thirty-three of 164 patients (63.6% women; median ages, 81.9±4.95 years) were included. Diagnostic aetiologies were: 42.9% Alzheimer disease, 30.8% Parkinson-dementia/Lewy body disease, and 15.8% vascular/mixed dementia. A total of 68.4% of patients had received other anti-psychotic drugs previously and 32.3% had ES due to antipsychotics. The AACU received were: quetiapine (76.7%), ziprasidone (18.8%), and olanzapine (4.5%). Median follow-uptime was 20.25±20.38 months. Side effects were observed in 19.7% of patients. Improvement of NPI (Neuropsychiatric Inventory) was 33.3±24.75 points. Agitation/aggressiveness (5.6±4.55), delirious ideas (4.94±5.07), irritability (4.38±4.94), and anxiety (4.32±4.83) were the symptoms that most improved. Although there were no differences between AACU, quetiapine was associated with significant maintenance in monotherapy (94.1% vs 72% for ziprasidone and 83.3% for olanzapine; $p<0.0001$).
Conclusions: AACU are effective and well tolerated drugs. Quetiapine was the most frequently used AACU. An excessive percentage of patients previously received other antipsychotics and present with ES.

* Corresponding author.
E-mail: diegosangar@yahoo.es (D. Santos-Garcia).

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PALABRAS CLAVE
Agitación;
Antipsicótico;
Demencia;
Neuroléptico;
Quetiapina;
Trastorno conductual

Análisis descriptivo de la prescripción de antipsicóticos atípicos de uso compasivo en el área sanitaria de Ferrol

Resumen
Objetivos: Aunque quetiapina y ziprasidona producen menos síntomas extrapiramidales (SEP) que otros antipsicóticos, su uso en pacientes mayores de 75 años con demencia se ve condicionado por la obligatoriedad de prescribirlos "por uso compasivo". Realizamos un análisis descriptivo del uso de antipsicóticos atípicos de uso compasivo (AAUC) en el área sanitaria de Ferrol.
Pacientes y métodos: Incluimos a todos los pacientes que recibieran un AAUC desde marzo de 2004 (fecha en que entró en vigor la dispensación de AAUC) hasta el 30-11-2008.
Resultados: Se incluyó a 133 de un total de 164 pacientes (el 63,6% mujeres; media±desviación estándar de edad, 81,9 ± 4,95 años). El 94,1%presentaba demencia (el 42,9% enfermedad de Alzheimer; el 30,8% demencia-enfermedad de Parkinson, y el 15,8% demencia vascular/mixta). El 68,4%había recibido algún otro antipsicótico previo y el 32,3%presentaba SEP secundarios. Los AAUC prescritos fueron: quetiapina (76,7%), ziprasidona (18,8%) y olanzapina (4,5%). La media de tiempo de seguimiento fue 20,25 ± 20,38 meses. El cumplimiento terapéutico fue del 95,5%. El 19,7%presentó efectos secundarios. La media de mejora en la escala NPI (Neuropsychiatric Inventory) fue 33,3 ± 24,75 puntos. La agitación/agresividad (5,6 ± 4,55), las ideas delirantes (4,94 ± 5,07), la irritabilidad (4,38 ± 4,94) y la ansiedad (4,32 ± 4,83) fueron los síntomas que más mejoraron. Aunque no hubo diferencias entre los 3 AAUC, quetiapina conllevó un mayor mantenimiento en monoterapia (el 94,1 frente al 72%de ziprasidona y el 83,3%de olanzapina; $p < 0,0001$).
Conclusiones: Los AAUC son fármacos efectivos y bien tolerados. Quetiapina es el AAUC más utilizado. Un porcentaje excesivo de pacientes reciben antes otros antipsicóticos y presentan SEP.

Introduction

Neuroleptics are drugs commonly used in neurology for the control of behavioural symptoms in patients with dementia; in particular, atypical antipsychotics (AA) stand out due to their reduced ability to induce or exacerbate extrapyramidal symptoms (EPS). Risperidone presents a pharmacological profile that is more similar to classical neuroleptics,[1] and finding cases of Parkinsonism secondary to it in consultation is commonplace. Ziprasidone, olanzapine, and, especially, quetiapine and clozapine are AA that cause less EPS.[2] In contrast, their prescription in all patients without a diagnosis of schizophrenia / manic episodes (in practice, in patients who are 75 or older) is conditioned by the requirement of processing its use as compassionate (currently classified as drugs in conditions other than those authorised within the regulations on the availability of drugs in special situations, RD 1015/2009 from 19th June, Chapter III). This is an obvious drawback, when we consider that many of the patients who require it are of advanced age, especially those with dementia and behavioural disorders. In this sense, clinical experience accumulated during the treatment of patients with cognitive impairment and behavioural disorders probably points towards a predominant initial use of classical neuroleptics or risperidone among AA.

This article presents a detailed descriptive analysis of the use of AA prescribed by experts and administered to patients in the Ferrol health district by the Pharmacy Service of Hospital A. Marcide through compassionate use.

Patients and methods

We conducted an epidemiological, observational, non-interventionist, population, descriptive, retrospective study that included all patients who were receiving or had received one or more AA for compassionate use (AACU), administered by the Pharmacy Service of Hospital A. Marcide in Ferrol, from March 2004 (the date on which the dispensing of AACU was enforced) to 30 November 2008. The following exclusion criteria were considered: patients younger than 75 years, patients with unavailable information (in their history and/or registry of pharmacy data) required in the study for further analysis, and patients who refused (or their relatives did) to give informed consent to participate in the study.

As a hypothesis, we considered, according to our experience, that AACU were probably prescribed in a higher percentage of cases as a second option after others that had already caused EPS or other side effects or that had not been effective.

The main objective of the study was to carry out a descriptive analysis of the use of AACU prescribed in the health area of Ferrol and to learn the following data, among others: the most commonly prescribed drug, prescribing service, most frequent symptoms, most frequent diagnosis,

percentage of patients who had previously received other neuroleptic drugs, rate of patients who presented EPS, and data on AACU effectiveness, tolerability and safety. Carrying out a comparative analysis between the different types of AACU administered was considered a secondary objective, always taking into account the methodological limitations of this type of study and, furthermore, that it was not designed for this purpose.

The data for each patient were obtained from the information available in the medical history, from a data registry of the pharmacy service (DIPEX® outpatient dispensing software) and from interviews with relatives of patients. Scores on the MMSE scale (Mini-Mental State Examination), FAST (Functional Assessment Staging) and GDS (Global Deterioration Scale) were from the time when it was decided to prescribe the AACU. A member of the pharmacy service staff with clinical experience in the management of patients with dementia and behavioural disorders controlled the Neuropsychiatric Inventory (NPI) scale (0-144 points) before starting AACU treatment and between 4 and 6 months (at the least) after starting it. We quantified the percentage of improvement for each item on the NPI scale using the formula: [(NPI improvement / baseline NPI) × 100]. The improvement, both general and behavioural, experienced by patients with AACU treatment was evaluated through the opinion of the relative who was directly in charge of care; the following categories were considered: very notable improvement, notable, moderate, slight and no improvement. The diagnoses in the different types of dementia were established following the diagnostic criteria issued by the Study Groupfor Behavioural Neurology and Dementia of SEN.[3]

The Ethics Committee of Hospital A. Marcide in Ferrol approved the implementation of this study. It was also necessary to obtain informed consent from the patients or, alternatively, from one of their relatives.

Statistical analysis

The data were analysed using SPSS 15.0 statistical software. Quantitative variables were expressed as mean±standard deviation (SD). The qualitative variables were expressed as a percentage. The Student t test or ANOVA test were used to perform the comparative analysis of quantitative variables and the χ^2 test was used for qualitative variables. Values were considered significant at $p<0.05$.

Results

The study included 133 out of a total of 164 patients (63.2% women, with a mean±SD age of 81.92±4.85 years). Twenty-nine patients were excluded due to lack of information, while informed consent for participation was not granted by the family in 2 cases. Figure 1 shows the patient selection and monitoring data.

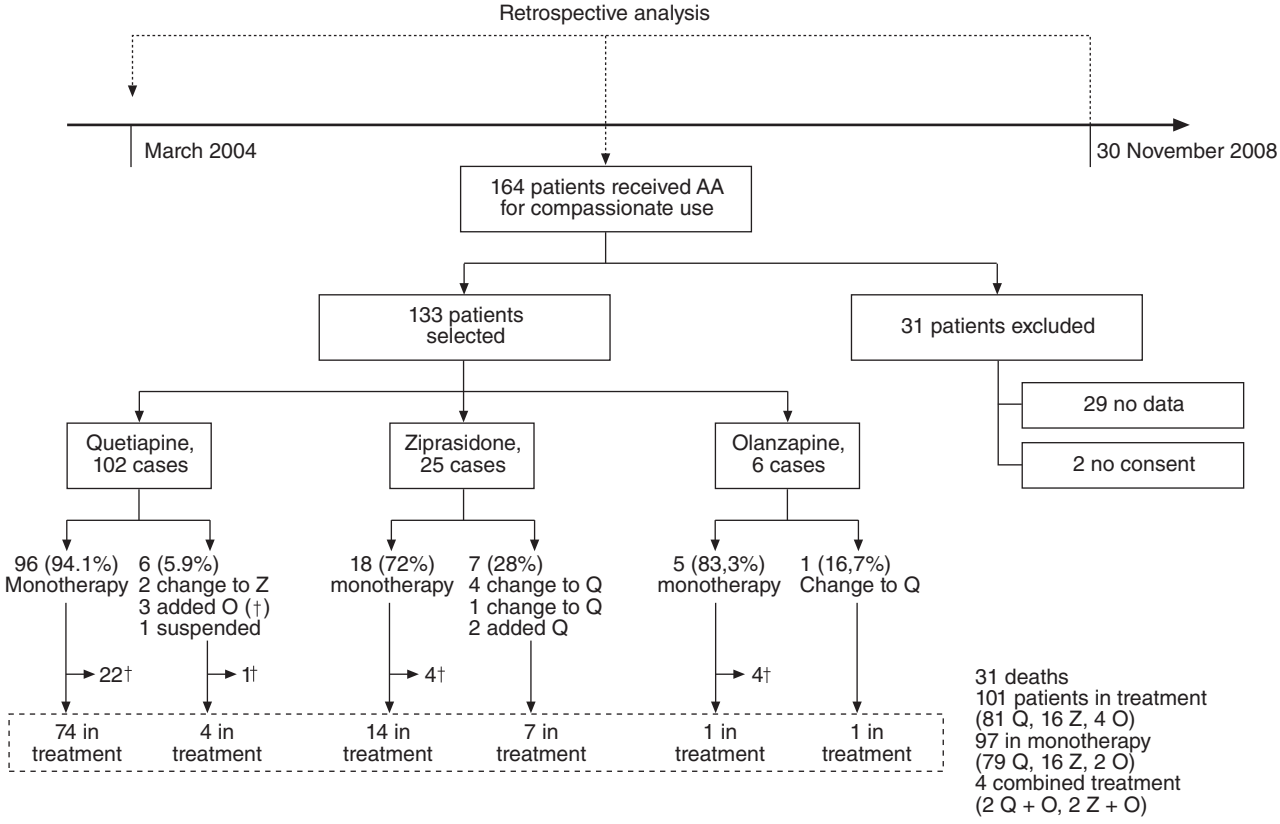

Figure 1 Selection and clinical course of patients in relation to the intake of atypical antipsychotics for compassionate use analysed. O: Olanzapine; Q: quetiapine; Z: ziprasidone.

Table 1 Baseline characteristics of the sample (n=133)

Age	81.92±4.85
Females	63.2
Type of life	
Living alone	2.3
Living alone with part-time caregiver	3
Living with spouse	20.3
Living with descendants and/or descendants and spouse	48.1
Living in nursing residence	6.8
Others	9.1
No data	10.4
Diagnosis	
Alzheimer disease-type Dementia	42.9
Vascular/mixed dementia	15.8
Dementia with Lewy bodies/Parkinson dementia	30.8
Frontotemporal dementia	2.3
Other dementias	2.3
Neurological diseases other than dementia	2.3
Others	3.6
Prescribing service	
Neurology	96.2
Psychiatry	3
Internal medicine	0.8
Others	0
Concomitant treatment	
Benzodiazepines	54.9
Donepezil	16.5
Rivastigmine	18.8
Galantamine	8.3
Memantine	7.5
ACEI + memantine	3
Tricyclic antidepressants	8.3
Heterocyclic antidepressants	18
SSRI or dual	30.1
MMSE	18.61±6.28
GDS scale	4.11±1.36
FAST scale	4.24±1.37

ACEI: Acetylcholinesterase Inhibitors; FAST: Functional Assessment Staging; GDS: Global Deterioration Scale; MMSE: Mini-Mental State Examination; SSRI: selective serotonin reuptake inhibitors.
The data express the percentage or mean±standard deviation.

Table 2 Characteristics related to the indication of atypical antipsychotics for compassionate use

Symptoms motivating prescription	
Delusions	50.4
Hallucinations	43.3
Agitation/aggressiveness	69.8
Depression/dysphoria	37.8
Anxiety	32.3
Euphoria/joy	6.3
Apathy/indifference	17.3
Loss of hygiene and personal care	12.6
Disinhibition	18.9
Irritability/instability	44.9
Altered motor behaviour	27.6
Sleepdisturbances	43.3
Alterations of appetite and eating disorders	18.9
Vagrancy	13.4
Prior administration of other neuroleptics	
No	31.6
Yes, a classical neuroleptic	33.8
Yes, risperidone	31.6
Yes, at least 2 or more	3
Main reason considered by the doctor for prescription	
First treatment option	25.6
Lack of effectiveness with other prior ones	29.3
Non pharmacological EPS	12
DIPdue to prior neuroleptics	32.3
Secondary effects other than EPS	0.8
EPS prior to administration	
No	34.6
Yes, DIPdata	42.9
Yes, non-pharmacological EPS other than PD	5.3
Yes, PD	17.2

DIP: drug-induced Parkinsonism; EPS: extrapyramidal symptoms; PD: Parkinson's disease.
The data are expressed as a percentage.

Table 1 shows the baseline characteristics of the sample. 96.2% of the AACU were prescribed by a neurologist. As to diagnosis, 94.1% of patients who were prescribed AACU had some type of dementia; the most frequent etiologies were Alzheimer's disease (AD) (42.9%), dementia associated with Parkinson's disease (D-PD) or dementia with Lewy bodies (DLB) (30.8%), and vascular or mixed dementia (V-MD) (15.8%). In relation to other concomitant treatments, 54.9% received benzodiazepines, 54.1% cholinesterase inhibitor and/or memantine, and 56.4% some antidepressant.

Table 2 shows data related to the indications for AACU. The most common symptoms shown by patients at the time of prescribing AACU were agitation and/or aggression (69.8%), delusions (50.4%), irritability (44.9%), hallucinations (43.3%) and sleepdisturbances (43.3%). 68.4% of patients had previously received at least one other antipsychotic drug; risperidone was the most frequent (31.6%). 42.9% presented drug-induced Parkinsonism (DIP); in 75.3% of them, it was DIPsecondary to neuroleptics.

As for the type of AACU administered, the most frequent was quetiapine (76.7%), followed by ziprasidone (18.8%) and olanzapine (4.5%). The average AACU evolution follow-upperiod was 20.25±20.38 months. The average maintenance dose was 183.11±136.83 (range, 25-600) mg/day for quetiapine, 71.32±65.37 (range, 20-120) mg/day for ziprasidone and 6±2.24 (range, 5-10) mg/day for olanzapine. The initially scheduled AACU treatment was maintained by

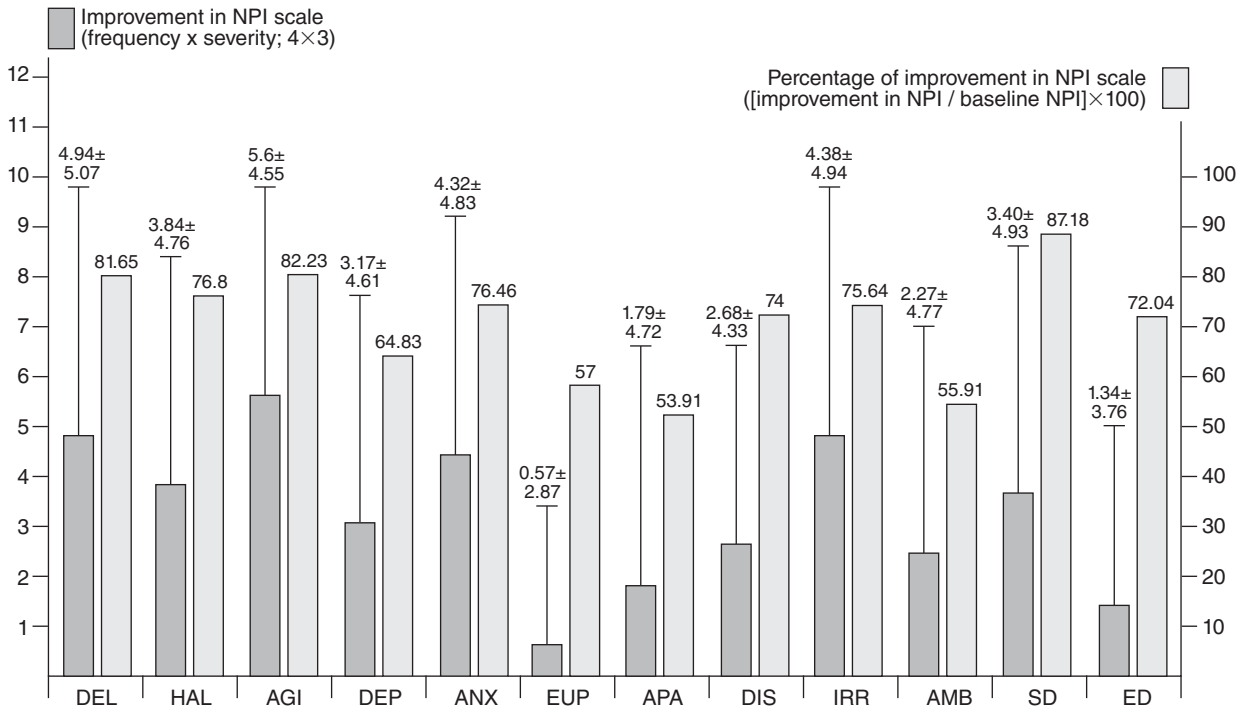

Figure 2 Improvement of various behavioural symptoms included in the NPI expressed in absolute terms (frequency × severity= 4 × 3 [0-12]) and as a percentage of improvement over the baseline severity of each symptom [(improvement in NPI / basal NPI) × 100]. AGI: agitation; AMB: abnormal motor behaviour; ANX: anxiety; APA: apathy; DEL: delusions; DEP: depression; DIS: disinhibition; ED: eating disorders; EUP: euphoria; HAL: hallucinations; IRR: irritability; SD: sleepdisorders.

89.5% of patients as monotherapy without receiving other antipsychotic drugs. Side effects were experienced by 19.7% of patients; the most common were drowsiness (7.6%) and agitation / paradoxical effect (3.8%). 23.3% of the patients died.

With regard to patient improvement, 84.3% presented some degree of behavioural improvement (49.7%, important to very important improvement) and 75.3% general improvement (25.6% improvement to very important improvement). The mean NPI scale improvement was 33.3±24.75 points. The symptoms that improved the most were agitation/aggression (5.6±4.55), delusions (4.94±5.07), irritability (4.38±4.94), anxiety (4.32±4.83), hallucinations (3.84±4.76) and sleepdisorders (3.4±4.93) (table 3 and fig. 2).

The comparative analysis between the three AACU administered showed no differences in behavioural and general improvement experienced, nor in the NPI score (table 4). Quetiapine was associated with a higher percentage of cases maintained in monotherapy (94.1%) compared to ziprasidone (72%), and olanzapine (83.3%) ($p<0.0001$). The average follow-upperiod (in months) for patients receiving olanzapine was higher (48.5±20.39) compared to ziprasidone (23.5±20.19) and quetiapine (17.79±19.09) ($p<0.001$). Side effects were experienced by 19.7% of patients. Two patients (1.9%) who received quetiapine presented severe adverse events (one, stroke, and the other, acute myocardial infarction) and one (4%) who received ziprasidone (acute renal failure), compared with 2 patients (33.3%) among those who received olanzapine (one ischemic stroke, and the other peripheral arterial thrombosis) ($p=0.007$).

Discussion

This study presents a retrospective analysis on the use of AACU administered in our health area until November 2008. This analysis shows that AACU are drugs likely to be effective and well tolerated by patients with psychotic and/or behaviour disorders associated with dementia.

One of the features of the new generation AA is their reduced ability to induce or exacerbate EPS. This property is associated with their decreased activity on D2 dopamine receptors in the striatum and their ability to act as serotonin 5HT2A receptor antagonists, resulting in a reduced rate of Parkinsonism, with good psychotic symptom control. Quetiapine[4] and clozapine (rarely used, because it produces agranulocytosis in 2% of cases and therefore requires periodic haematological controls[5]), and to a lesser extent ziprasidone[6] and olanzapine,[7] are especially less causative of Parkinsonism. In contrast, risperidone has a similar pharmacological profile to that of classical neuroleptics and frequently produces Parkinsonism.[1] Recently commercialised, paliperidone is a metabolite of risperidone that is potentially less causative of Parkinsonism and that has proven effective in controlling psychotic symptoms in different schizophrenia studies;[8] its results as an antipsychotic in daily practice have yet to be examined. Other AA agents, such as amisulpride, aripiprazole, sertindole or zotepine, are not commonly used in patients with dementia and behaviour disorders.

The drawback is that in our country, with the exception of risperidone (the only AA approved for the treatment of behavioural and psychological symptoms of dementia by

Table 3 Characteristics related to the administration of atypical antipsychotic (AA) for compassionate use

AA administered as a first option	
Quetiapine	76.7
Ziprasidone	18.8
Olanzapine	4.5
Maintenance of treatment	
AA maintained in monotherapy	89.5
Changed by another and associated to a second AA	10.5
Evolution time with AA (months)	20.25±20.38
Average maintenance daily dose (mg/day)	
Quetiapine	183.11±136.83
Ziprasidone	71.32±65.37
Olanzapine	6±2.24
Therapeutic compliance	95.5
Behavioural improvement (caregiver)	
Very notable improvement	21.1
Notable improvement	28.6
Moderate improvement	18.8
Slight improvement	15.8
No improvement	15.7
General improvement (caregiver)	
Very notable improvement	4.5
Notable improvement	21.1
Moderate improvement	27.1
Slight improvement	22.6
No improvement	24.7
NPI scale (before AA)	50.17±24.25
NPI scale (after AA)	16.86±16.64
Improvement in NPI (total)	33.3±24.75
Delusions	4.94±5.07
Hallucinations	3.84±4.76
Agitation/aggressiveness	5.6±4.55
Depression/dysphoria	3.17±4.61
Anxiety	4.32±4.83
Euphoria/joy	0.57±2.87
Apathy / indifference	1.79±4.72
Disinhibition	2.68±4.33
Irritability/instability	4.38±4.94
Altered motor behaviour	2.27±4.77
Sleep	3.40±4.93
Eating disorder	1.51±3.76
Severe adverse events	3.7
Deaths	23.3
Secondary effects	19.7
Somnolence	7.6
Dyskinesias	1.5
Agitation / paradoxical effect	3.8
Others	6.8

NPI: Neuropsychiatric Inventory.
Data expressed as a percentage or mean±standard deviation.

the Spanish Drug Agency), the prescription of quetiapine, olanzapine and ziprasidone in patients over 75 years with dementia and behaviour disorders must be for compassionate use. In these cases, the prescribing physician assumes, under his sole responsibility, their use for an indication other than those authorised (Medicines Act, Article 23 of the Royal Decree). The use of a drug for compassionate use requires the written informed consent of the patient or his legal representative, a clinical report in which the physician justifies the need for such treatment, the approval of the director of the centre where the treatment is to be applied and the authorisation of the Pharmacy and Health Products General Management for each specific case. In many cases, these requirements condition the prescription of antipsychotics for patients over 75 years with behavioural disorders associated to dementia, with the corresponding risk of administering antipsychotics that do not require compassionate use, but have more side effects (especially, EPS). In our series, out of 133 patients (94.1% with some type of dementia), 91 (68.4%) had previously received at least one other antipsychotic (risperidone in 31.6% of cases) and upto 32.3% presented secondary EPS. This could be due to the fact that many patients arrive at the neurology specialist consultation from primary care or from other specialists having less knowledge in the management of antipsychotic drugs and/or inability to prescribe AACUs, and even to a frequent prescription by the neurologists of risperidone as the initial AA (the data on which doctor ordered the antipsychotic/s previously received by the patient were not collected). However, in the analysis by diagnostic groups, up51.2% of patients with D-PD/DLB had not received any prior antipsychotics (the AACU was the first antipsychotic treatment option for the control of behavioural symptoms), compared with 21.1% of those suffering AD or with the 19% suffering V-MD (p=0.049; data not shown.) This indicates a refusal to treat with antipsychotic drugs that may potentially induce Parkinsonism (without the need to be prescribed for compassionate use) for PD patients and, conversely, their more frequent administration as first option in patients with dementia and behavioural disorder but without EPS. The problem is that, in the long term, the functional status of these patients worsened due to side effects caused by these drugs and many of them presented EPS when we prescribed AACU.

In relation to the sample characteristics, 94.1% of patients who received AACU presented dementia. Of the 8 patients without dementia, 5 presented behavioural alterations with no criteria of dementia; 2 presented behavioural disorders associated with cerebrovascular disease, and 1 presented refractory headache. In terms of type of dementia, the high percentage of patients with D-PD/DLB (30.8%) is striking, compared with the normal distribution (AD, 50-70%; VD, 15-27%; DLB, 10-15%; and D-PD, 5-8%[8-11]). This is most likely explained by the fact that patients with D-PD/DLB frequently present psychotic disorders, hallucinations, depression, anxiety and other symptoms, both in relation to the treatment and to their PD, which condition the need for antipsychotics in many cases. Although FTD often involves behaviour problems requiring neuroleptics, only 3 patients in our series presented FTD. The low prevalence of FTD and the onset of the disease between 45 and 64 years[12] could explain this. A higher score on the FAST scale was also associated with a higher score on the NPI scale (positive correlation, power of 0.197; p=0.044. In the case of the GDS scale and MMSE, we observed a trend towards positive and negative correlation

Table 4 Comparison between the atypical antipsychotics (AA) used (n=133)

	Quetiapine (n=102)	Ziprasidone (n=25)	Olanzapine (n=6)	p
Age	81.96±4.96	82.08±4.05	80.5±6.53	0.763
Females	58.82	80	66.67	0.142
Maintenance of treatment				<0.0001
AA maintained in monotherapy	94.1	72	83.3	
Changed for another or associated to a second AA	5.9	28	16.7	
Time of evolution with the AA (months)	17.79±19.09	23.5±20.19	48.5±20.39	<0.001
Therapeutic compliance	95.09	96	100	0.846
MMSE	17.12±6.63	19.29±4.49	12.2±4.1	0.032
FAST scale	4.9±1.31	4.6±1.57	5.2±1.59	0.019
GDS scale	4.1±1.3	4.05±1.5	4.63±1.39	0.033
Behavioural improvement (caregiver)				0.242
Very notable improvement	19.6	24	33.3	
Notable improvement	28.4	20	66.6	
Moderate improvement	18.6	24	0	
Slight improvement	14.7	24	0	
No improvement	18.7	8	0	
Notable to very notable improvement	48	44	100	
General improvement (caregiver)				0.306
Very notable improvement	5.9	0	0	
Notable improvement	20.6	16	50	
Moderate improvement	24.5	32	50	
Slight improvement	22.5	28	0	
No improvement	26.5	24	0	
NPI scale (before AA)	52.35±23.07	49.93±32.11	39.5±4.95	0.743
NPI scale (after AA)	17.87±17.15	12.79±15.38	16.5±6.36	0.601
Improvement in NPI (total)	33.45±22.71	34.14±34.29	23±1.41	0.844
Delusions	4.86±5.01	6.3±5.44	—	0.273
Hallucinations	3.88±4.86	4.1±4.79	2±2.83	0.852
Agitation / aggressiveness	5.61±4.6	5.5±4.38	6±2.83	0.99
Depression / dysphoria	3.18±4.67	3.6±4.81	1±1.41	0.773
Anxiety	4.35±4.62	4.6±6.45	2±2.83	0.785
Euphoria / joy	0.78±2.44	2.2±4.64	—	0.343
Apathy / indifference	2.14±4.58	0.1±4.77	1.5±2.12	0.464
Disinhibition	2.53±4.41	3.1±4.95	4.5±4.95	0.781
Irritability / instability	3.98±4.91	6.3±5.44	5±4.24	0.398
Altered motor behaviour	2.29±4.41	2.6±5.23	—	0.784
Sleep	3.33±4.51	4.2±5.53	1±1.41	0.695
Eating disorder	1.61±3.69	1.3±2.9	—	0.828
Severe adverse events	1.9	4	33.3	<0.0001
Deaths	22.6	19.1	66.7	0.029
Secondary effects	20.6	12.5	33.3	0.364
Somnolence	8.82	4.16	0	

The data express the percentage or mean±standard deviation.

respectively with NPI, but without reaching statistical significance; data not shown). Interestingly, this was not the case with patients in the olanzapine group(only 6 patients); these patients, despite presenting higher scores on the FAST and GDS scales and lower scores on the MMSE, had a lower score on the NPI. This points out the obvious: that the greater the degree of cognitive impairment, the greater the likelihood of behavioural change in different types of dementia. This is a well known fact, especially in AD, in which behavioural disorders typically occur at advanced stages of the disease.[13]

As for the type of life, only 6.8%of the total sample lived in a nursing home, and upto 68.4%lived in the company of another person. With regard to concomitant treatment, 57.6%of patients with dementia (53 of 125 patients) were receiving a cholinesterase inhibitor and/or memantine. This is perhaps a small percentage, if we consider that donepezil,[14,15] rivastigmine,[16] galantamine[17] and memantine[18,19] have proven effective in controlling different behavioural symptoms in patients with dementia in different studies. This fact, coupled with their good tolerability, enables us to delay the use of neuroleptics (which are

always tolerated worse and have more side effects). The percentage of patients treated with benzodiazepines (55.2%) and antidepressants (56.8%) in the groupwith dementia is consistent with other series.[20]

Quetiapine was without doubt the most widely used AACU in our series (102 patients), followed by ziprasidone (25 patients) and olanzapine (6 patients). There was a considerable improvement in both behavioural and general symptoms, according to the opinions of family caregivers of patients. The NPI scale was used to assess behavioural symptoms in relation to current recommendations.[21] This scale showed that the psychotic/behavioural symptoms that improved most were the positive symptoms (delusions, hallucinations, aggression, irritability and anxiety) especially, while some negative symptoms such as apathy hardly improved. However, since the improvement in the various items of the NPI scale in absolute terms is conditioned by the baseline score for each item, we also analysed the percent improvement ([NPI improvement / baseline NPI] × 100]) for each symptom. In percentage terms, the most improved behavioural symptoms were sleepdisorders. These results are consistent with other series.[22-24]. In this sense, olanzapine has proven effective in improving anxiety and hallucinations with doses of 5 mg/day.[25,26] Quetiapine has proven to be safe and effective in the long-term treatment of psychosis from various causes in elderly populations (average dose 137.5 mg/day),[27] in patients with psychosis associated with PD (doses between 25 and 75 mg/day)[28-30] and in patients with DLB.[31] Although there is less experience with ziprasidone, various studies have shown that it improves agitation, depression and psychosis in elderly patients with dementia.[32,33]

Of course, bearing in mind that this is a retrospective analysis and that the study was not designed with this intention, the data concerning the comparison between quetiapine, ziprasidone and olanzapine in our series should be viewed within the appropriate limitations (102 patients received quetiapine and only 6, olanzapine). Although there were no differences in terms of effectiveness, quetiapine was associated with a higher percentage of cases in monotherapy ($p<0.0001$). There was generally good tolerance and treatment compliance; drowsiness was the most common side effect (10 cases). Other side effects reported were agitation/paradoxical effect (5 cases), dyskinesia (2 cases), tremor (1 case), akathisia (1 case), excessive weight gain (1 case) and mouth dryness (1 case). Five patients (3.7%) presented serious adverse events (two of them, ischemic stroke) while receiving AACU. Although the appearance of these events was significantly associated with olanzapine, it should be noted that only 6 patients received olanzapine (and therefore just one case in this groupaccounts for as much as 16.6%). There was also a higher percentage of deaths in this group, but the causes of death were not analysed. These data are also probably conditioned by the fact that the follow-uptime with AACU in the olanzapine groupwas higher compared to quetiapine and ziprasidone and, more importantly, that the patients who received olanzapine presented a more advanced state of dementia (assessed through the MMSE, FAST and GDS scales). In a recent meta-analysis of 15 clinical trials (12 weeks duration) on AA in patients with dementia, there was a mortality rate of 3.5% in the grouptreated with AA compared to 2.3%of those treated with placebo, although the excess mortality was not examined individually in each case.[34] Well-designed studies should be conducted to clarify whether there is a risk of death and, if so, to quantify it (and its causes) in elderly patients receiving AA.

This study has important limitations. It is a retrospective analysis and not a prospective, double-blind study, designed to assess the effectiveness of AACU. Therefore, data on effectiveness and safety must be considered within that context. The groups established with respect to the type of AACU received varied too widely in the number of patients treated, for comparisons to be established. The cause of death was not analysed and neither was the development of Parkinsonian symptoms in the groupof patients who suffered EPSbefore receivingAACU(although the overall improvement was recorded according to a survey on the cohabitating relative). The categorisation of the degree of improvement experienced with the AA, both general and behavioural, did not take into account the possibility of worsening as one of the options (this was included in the "no improvement" group). Other possible treatment modifications that could influence the changes in the NPI scale after receiving AACU were not taken into account. Neither was the stress load of the caregiver assessed. Conversely, as a favourable aspect, it should be noted that this is a sample with a high number of patients, which allows us to extract interesting facts about AACU management in patients 75 years or more who require them. These can be considered as a good treatment option in patients with dementia and symptoms such as sleepdisturbances, agitation, delusions, hallucinations, anxiety or irritability.

In conclusion, the data from this study showed that AACU are effective drugs that are well tolerated in patients 75 years or older with dementia and concomitant behaviour disorder. An excessive proportion of patients received other prior antipsychotics and many presented secondary EPS. We propose that perhaps AACU should be used as first-line drugs to control behavioural symptoms and/or psychosis in these patients, ahead of other antipsychotic drugs with more side effects.

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Conflict of interests

The authors declare no conflict of interests.

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